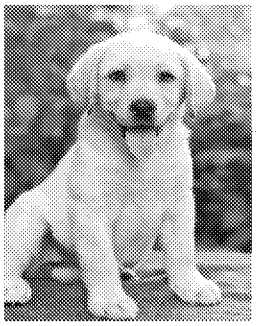


Proposed Seresto - Flumethrin + Imidacloprid Mitigation

2020

Briefing for the RD/PRD-IO

Purpose

The purpose of this briefing is to present options that address the incidents reported on the pet collar Seresto (Reg. No. 11556-155).

Seresto Background

Bayer is the manufacturer of Seresto, which was registered in 2012. The active ingredients are imidacloprid (10%) and flumethrin (4.5%).

The collar can be marketed for all sizes of cats, small dogs, and large dogs for treatment against fleas, ticks, and lice.

Incident Concerns

Seresto is a popular dog and cat collar that produces a large amount of reported incidents.

Common pet incidents that are reported:

-Neurological Damage/Seizures

-Hair/Skin Adverse Effects (Rash, Redness, Hair Loss and etc.)

-Death

Human Incidents are also reported

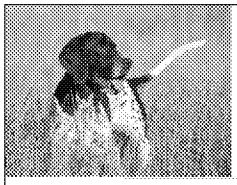
Incident Data Capturing

- At the discretion of consumers, concerns are submitted through a controlled portal, that is hosted by Bayer. From there, reports are submitted to EPA's proprietary incident data system.

- Regulations (Per PR notice 98-3), establish different requirements for reporting timeframes and for content of incident reports depending on the defined severity categories.

- Bayer also provides quarterly reports, which are distributed to the 6A2 Coordinator, who issues those reports to their designated departments (EFED/HED).

- Severity categories are defined in PR Notice 98-3 and supplemental documentation, known as the Exposure Type Severity Category Codes for Incidents.



PMRA Analysis

With permission from Bayer, EPA and PMRA coordinated a review of US incidents between 2012-2015 during PMRA's review of an application to register the product. PMRA reported the following:

Ex. 4 CBI

- PMRA considers an incident rate greater than **1 per 10,000** units sold an indicator of a potential problem

Ex. 4 CBI

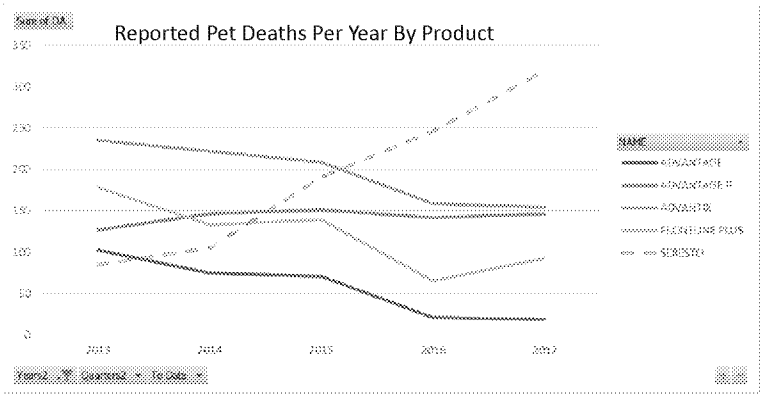
- The report examined incidents on both human applicators and domestic animals

- Seresto is not registered in Canada.

FYI According to the Health Canada label search flumethrin/Seresto was never registered in Canada as a pet collar https://pr-rp.hc-sc.gc.ca/ls-re/index-eng.php
-THUS Canada never had their own incidents, they just reviewed what they received from Bayer.

Further Analysis

- Imidacloprid, flumethrin and fipronil make up 67% of pet incidents reported between 2012 and 2017.
- Trends over time were compared for the years 2013 to 2017 (Seresto came on the market about 2012).
- The Seresto collar only has one registration number for all sizes and species for which the collar is formulated (large dogs, small dogs and cats). In order to make consistent comparisons between products, products were combined for all pet sizes

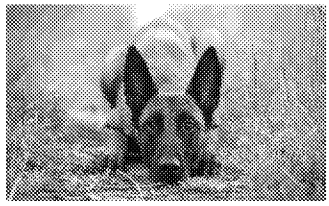


Ex. 5 Deliberative Process (DP)

Historical Incident Analysis/Casualty Report

- Listed below, is aggregate summary results for Seresto (Small Dogs) for 2019.

N	O	P	Q	R	S	T
Total Inci	HD	HE	DA	DB	DC	DCDE
3019	24	0	81	21	0	2893
1669	25	0	70	13	0	1561
4651	44	0	151	30	0	4426
31	2	0	2	0	0	27
1157	7	0	14	2	0	1134
168	4	0	8	2	0	154
2511	10	0	24	14	0	2463
3	0	0	0	0	0	3
1476	6	0	4	5	0	1461



HD – human minor severity.
HE – human no or unknown effects.
DA – domestic animal death.
DB- domestic animal major severity.
DC - domestic animal moderate severity.
DCDE – domestic animal moderate, minor, no or unknown effects grouped together.

- Total number of incidents (Column N) – 14,685

6a2 Incident Data Capturing

- Current EPA incident reporting does not tie incidents to sales data; we do not know how the number of incidents corresponds to the number of products sold.
- At the discretion of consumers, concerns are submitted through Bayer's controlled portal.
- From there, reports are submitted to EPA's incident data system.

Submitted 6a2 Data Shortcomings

1. The aggregate data and portal submission systems, do not have the ability to differentiate between each incident.
2. We cannot connect incident reporting with corresponding sales data.
3. No standard threshold that determines how many incidents are needed to consider this product "unsafe."
4. Data are distributed to either EFED and HED, which are not tasked to observe pet incidents. No one is dedicated to the review of pet data.
5. Details of the incident are not provided, making identifying any mitigation to help address issues very difficult.

Required to submit all data

Precedence for Enhanced Reporting-History – spot ons

In spring of 2009, due to an increase in reports of pet incidents involving spot-on products, EPA started requesting enhanced incident data.

As a result of the review of incident data received, EPA implemented the following measures:

- Label mitigation to clarify instructions for safe use and to prevent misuse
- Limitation on Confidential Statements of Formulations (CSFs) to one formulation.
- 2-year time-limited conditional registrations that necessitated quarterly enhanced reporting.

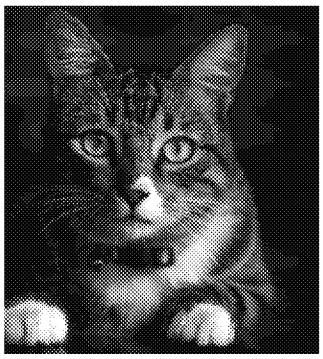
There are two standardized templates that encompass enhanced reporting: incident and sales.

RD has a long history with spot-on products as a result of work done back in 2008-2009. Around that time, EPA received a number of incidents associated with pet spot-on products. This resulted in EPA sending out letters to 19 companies requesting implementation of several measures, including 2-year time-limited conditional registration requirements, label mitigation clarifying use instructions, a limit on CSFs to one formulation, and a requirement for enhanced quarterly incident reporting with sales data.

Historical Seresto Registrant Correspondence

EPA has recently reached out to Bayer to discuss the large number of reported incidents. Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)



European mitigation is as follows:

1) Mild application site reactions such as pruritus, erythema and hair loss may occur. These have been reported as rare and usually resolve within 1 to 2 weeks without the need for collar removal. In single cases, a temporary collar removal may be recommended until the symptoms have disappeared. In very rare cases, application site reactions such as dermatitis, inflammation, eczema or lesions may occur and in these instances, collar removal is recommended. In rare cases neurological symptoms as ataxia, convulsions and tremor may occur. In these cases collar removal is recommended. Also in rare cases in dogs, slight and transient reactions as depression, change of food intake, salivation, vomiting and diarrhea might occur initially.

2) This product should not enter water courses as it may be dangerous for fish and other aquatic organisms.

3) Separate registration for dogs and cats.

Note> https://www.vetsend.co.uk/files/pdf/leaflet-seresto-dog-2.pdf

Risk Analysis and Management Considerations

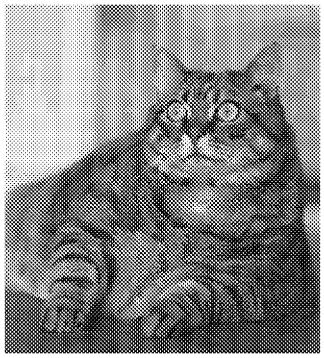
Ex. 5 Deliberative Process (DP)

Next Steps

Ex. 5 Deliberative Process (DP)

Short-Term *Proposed* Mitigation

Ex. 5 Deliberative Process (DP)



Cathryn Britton/Melanie Biscoe – There was also discussion on **Ex. 5 Deliberative Process (DP)** **Ex. 5 Deliberative Process (DP)** Has this ship already sailed? What are your thoughts?

Long-Term *Proposed* Options

Ex. 5 Deliberative Process (DP)

(40 CFR 159.195 (c)). "The registrant shall submit to the Administrator information other than that described in 159.165 through 159.188 if the registrant has been informed by EPA that such additional information has the potential to raise questions about the continued registration of a product or about the appropriate terms and conditions of registration of a product."

Ex. 5 Deliberative Process (DP)

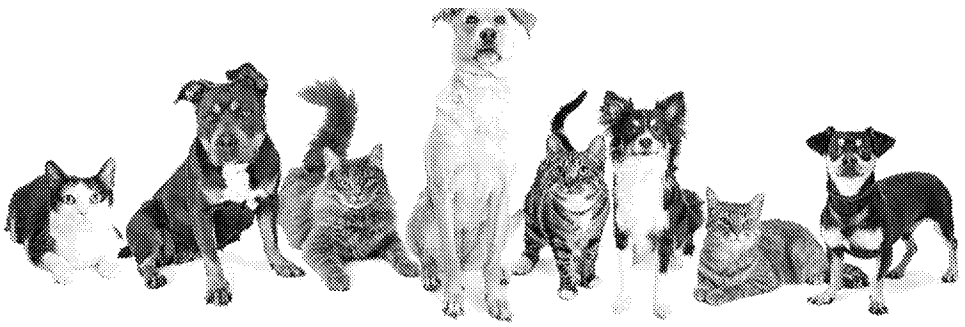
Recommendations

- Immediately:

Ex. 5 Deliberative Process (DP)

- Long Term:

Ex. 5 Deliberative Process (DP)



Thank You! Questions?

Supplemental Slides

Potential Path Forward – **Ex. 5 Deliberative Process (DP)**

Ex. 5 Deliberative Process (DP)

Potential Path Forward –

Ex. 5 Deliberative Process (DP)

Potential Path Forward – **Ex. 5 Deliberative Process (DP)**

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Potential Path Forward — Ex. 5 Deliberative Process (DP)

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Ex. 5 Deliberative Process (DP)

The Big Picture of available information

Why focus on spot-on and collars?

Ex. 5 Deliberative Process (DP)